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36. The antibody of claim 1, which is a monoclonal antibody.

37. The antibody of claim 1, which is a humanized antibody.

REMARKS

Reconsideration of the application in view of the above amendments and following remarks is requested. Claims 32-37 are now in the case. Claims 27 and 29-31 have been cancelled. No new matter has been added.

Support for new claims 32-37 is found within the specification as filed, such as at pages 10, 19-20, 33-35, and elsewhere.

The specification has been amended to replace the title of the invention and the abstract of the disclosure, and to remove the embedded hyperlink. Copies of the amended sections of the specification, marked to show changes, are included in the enclosed Appendix.

Claims 27 and 29-31 were rejected under 35 U.S.C. § 112, first paragraph. The Office believes that these claims are not fully enabled and that these claims contain subject matter which is not sufficiently described in the specification.

Applicant believe that the rejections under § 112, first paragraph have been obviated by the cancellation of claims 27 and 29-31. New claims 32-37 clearly recite that the antibody specifically binds to a polypeptide as shown in SEQ ID NO:2 from residue 1 through residue 373, a polypeptide as shown in SEQ ID NO:15 from residue 1 through residue 373, or a polypeptide as shown in SEQ ID NO:18 from residue 1 through residue 364. The Office has acknowledged that such antibodies are enabled by Applicant's specification (Office Action at page 2). The recited antibodies are also fully described within the specification.

The Office has denied priority to Application No. 09/072,384 and Provisional Application No. 60/044,185.

Applicant respectfully traverses the denial of his priority claim. The present application is a divisional of Application No. 09/072,384 (the '384 application), and, as filed, is a copy of the '384 application. Thus, whatever is disclosed in the present application must also have been disclosed in the '384 application. As to the specific, contested subject matter, the proteins of SEQ ID NO:15 and SEQ ID NO:18 are disclosed in the '384 application at page 19, line 19 through page 20, line 22, as well as in the Sequence Listing. It is disclosed at pages 19-20 that these sequences are zsig13 sequences. The specification further discloses, at pages 33-34, that zsig13 proteins and protein fragments can be used "to prepare antibodies that specifically bind to zsig13 proteins" (page 33, lines 33-35) One of ordinary skill in the art would readily

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comprehend that the "zsig13 proteins" referred to at page 33 include the zsig13 proteins of SEQ ID NO:15 and SEQ ID NO:18.

Claims 27 and 29-31 were rejected under 35 U.S.C. § 102 (b). The Office believes that the claims are anticipated by U.S. Patent No. 5,460,953 as evidenced by Bost et al. and Bendayan. The Office believes that the '953 patent "teaches monoclonal antibodies against recombinant and wild-type human zymogen protein C" and that, "[a]lthough the reference is silent about the antibody binding to residues 1-373 or 111-373 of SEQ ID NOS: 2 and 15, or residues 111-364 or 1-364 of SEQ ID NO:18, it does not mean that the reference antibody does not bind to these sequences." Bost et al. and Bendayan have been cited to show antibody cross-reactivity.

Applicant respectfully traverses this ground of rejection. The '953 patent does not teach or suggest an antibody that specifically binds to a polypeptide as shown in SEQ ID NO:2, SEQ ID NO:15, or SEQ ID NO:18. In the absence of some actual teaching of such an antibody, the instant rejection must be based on inherency. Indeed, the case law cited by the Office in support of the rejection, insofar as it addresses novelty under Section 102, is directed to the question of inherency. For the reasons discussed below, a rejection based on inherency cannot be sustained.

The standard for anticipation (lack of novelty) under Section 102 is one of strict identity. To anticipate a claim, a single reference must contain all its essential elements. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 90 (Fed. Cir. 1986) ("It is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention, and that such a determination is one of fact."); *In re Donohue*, 766 F.2d 531, 226 USPQ 619, 621 (Fed. Cir. 1985) ("an anticipation rejection requires a showing that each limitation of a claim must be found in a single reference, practice, or device."); *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 808 F.2d 1471, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986) ("Under 35 U.S.C. § 102, anticipation requires that each and every element of the claimed invention be disclosed in a prior art reference."). To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.*, 334 USPQ2d 1565 (Fed. Cir. 1995). Further, to serve as an anticipation when a reference is silent about the alleged inherent characteristic, such gap in the reference may be filled by extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily (i.e., always) present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill in the art. *In re Oelrich*, 40 USPQ 323 (C.C.P.A. 1981); *Continental Can Co. USA v. Monsanto Co.*, 20 USPQ2d 1746 (Fed. Cir. 1991). Inherency must be certain. *Ex parte Cyba*, 155 USPQ 756, 757 (Bd. Pat. App. Int. 1966). See also, *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 220 USPQ 303,

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314 (Fed. Cir. 1983) ("Anticipation of inventions set forth in product claims cannot be predicated on mere conjecture respecting the characteristics of products that might result from the practice of processes disclosed in references.").

To render the rejected claims unpatentable, the cited reference must disclose an antibody that necessarily (i.e., always) specifically binds to a polypeptide selected from the group consisting of a polypeptide as shown in SEQ ID NO:2 from residue 1 through residue 373, a polypeptide as shown in SEQ ID NO:15 from residue 1 through residue 373, and a polypeptide as shown in SEQ ID NO:18 from residue 1 through residue 364. The '953 patent contains no such disclosure. The term "specifically binding" to a zsig13 protein is defined on page 34 of the specification to mean that the antibody binds to the zsig13 protein with an affinity at least 10-fold greater than the biding affinity to a non-zsig13 protein. Thus, to anticipate Applicant's claims, the teachings of the '953 patent must always result in an antibody that binds to a zsig13 protein with an affinity at least 10-fold greater than its binding affinity to human protein C.

The references relied upon by the Office as extrinsic evidence do not support the rejection. Rather, these reference clearly teach that the certainty that is essential to a rejection based on inherency is absent. Bandayan discloses that an anti-glucagon antibody did not stain insulin-secreting cells (Figure 1), thereby demonstrating that cross-reactivity is not a necessary and inherent property of antibodies. It is known in the art that antibody cross-reactivity is the exception rather than the rule. See, for example, Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988 at page 24 (copy enclosed): "Because antibodies can recognize relatively small regions of antigens, occasionally they can find similar epitopes on other molecules." [Emphasis added.]

The Office also appears to have assumed that if an antibody to protein C recognizes the sequence Val-Leu-Thr-Ala-Ala-His-Cys within protein C, it will also recognize that sequence within Applicant's protein. However, as disclosed by Goldsby et al. (*Kuby Immunology*, Fourth Edition, W.H. Freeman and Company, New York, 2000), the art is not so predictable:

> "[S]tudies have revealed that 15-22 amino acids on the surface of the antigen make contact with a similar number of residues on the antibody's binding site; the surface area of this large complementary interface is between 650Å^2 and 900Å^2. For these globular protein antigens, then, the shape of the epitope is entirely determined by the tertiary conformation of the native protein." [Id., 68-69. Copy enclosed.]

Thus, the mere presence of a common sequence of seven amino acid residues is not a sufficient basis for predicting cross-reactivity; the context of that sequence within the

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larger protein is determinative. From fifteen to twenty-two residues will actually contact the antibody, and the conformation of this site is a function of the higher order structure of the protein. See also, Harlow and Lane (*ibid.*) at 26:

> "The specificity of antibodies has been demonstrated by a large number of experiments showing that small changes in the epitope structure can prevent antigen recognition."

In summary, the sequence identified by the Office does not define a complete antibody binding site.

The sequence identified by the Office as occuring in both Applicant's proteins and the '953 patent includes a large proportion of hydrophobic amino acid residues, including Val, Leu, and Ala. See, Lehninger, *Short Course in Biochemistry*, Worth Publishers, Inc., 1973 at page 37 (copy enclosed). However, as disclosed by Goldsby et al. at page 69, "The B-cell epitopes on native proteins generally are composed of hydrophilic amino acids on the protein surface that are topographically accessible to membrane-bound or free antibody." Thus, the region identified by the Office would not be expected to be antigenic.

The data of Bost et al. were obtained from studies using anti-peptide antibodies. However, the '953 patent does not teach or suggest raising anti-protein C antibodies by immunization with any peptide, much less the specific peptide cited by the Office. Even assuming, *arguendo*, that such a teaching were present in the combined references, the outcome asserted by the Office cannot be predicted.

> "The percentage of antibodies raised against peptides that will bind to the native protein will vary from antigen to antigen. Values reported in the literature range from 0/4 to 3/4 of anti-peptide antibodies will bind to the native antigen." [Harlow and Lane, *ibid.*, at 72-73.]

Thus, even anti-peptide antibodies raised against the common sequence (assuming, *arguedo*, that such antibodies could be raised) could not be predicted to bind to either protein C or zsig13, much less to <u>specifically bind</u> to a zsig13 protein.

Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 (b) are requested.

Claims 27 and 29-31 were rejected under 35 U.S.C. § 102(e). The Office believes that the claims are anticipated by U.S. Patent No. 5,712,143 as evidenced by Bost et al. and Bendayan. The Office believes that the '143 patent "teaches antibodies to flea serine protease proteins (i.e. SEQ ID NO: 16) comprising the amino acid sequence, Val Leu Thr Ala Ala His Cys Ile" and that, "[a]lthough the reference is silent about the antibody binding to residues 1-373 or 111-373 of SEQ ID NOS: 2 and 15, or residues 111-364 or 1-364 of SEQ ID NO:18, it does not mean that the reference

antibody does not bind to these sequences." Bost et al. and Bendayan were cited to show antibody cross-reactivity.

Applicant respectfully traverses this ground of rejection. The '143 patent does not teach or suggest an antibody that specifically binds to a polypeptide as shown in SEQ ID NO:2, SEQ ID NO:15, or SEQ ID NO:18. In the absence of some actual teaching of such binding, the instant rejection must be based on inherency. As such the rejection cannot be sustained.

The legal standard for establishing anticipation based on inherency has been discussed above. To render the rejected claims unpatentable, the cited reference must disclose an antibody that necessarily (i.e., always) specifically binds to a polypeptide selected from the group consisting of a polypeptide as shown in SEQ ID NO:2 from residue 1 through residue 373, a polypeptide as shown in SEQ ID NO:15 from residue 1 through residue 373, and a polypeptide as shown in SEQ ID NO:18 from residue 1 through residue 364. The term "specifically binding" to a zsig13 protein is defined on page 34 of the specification to mean that the antibody binds to the zsig13 protein with an affinity at least 10-fold greater than the biding affinity to a non-zsig13 protein. Thus, to anticipate Applicant's claims, the teachings of the '143 patent must always result in an antibody that binds to a zsig13 protein with an affinity at least 10-fold greater than its binding affinity to a flea serine protease protein.

The '143 patent contains no such disclosure. The '143 patent does not teach the use of small peptides to generate antibodies. In particular, the '143 patent does not teach or suggest using the sequence identified by the office as common to SEQ ID NO:16 of the '143 patent and Applicant's zsig13 proteins as an immunogen. For the reasons set forth above, immunization of an animal with the protein of '143 SEQ ID NO:16 or a peptide fragment thereof cannot be predicted to result in an antibody that binds to a zsig13 protein, much less an antibody that specifically binds to a zsig13 protein. Antibody cross-reactivity occurs "occasionally" (Harlow and Lane, *ibid.*). Epitopes comprise 15-22 amino acids and have a shape that is "entirely determined by the tertiary conformation of the native protein" (Goldsby et al. *ibid.*). "[S]mall changes in epitope structure can prevent antigen recognition" (Harlow an Lane, *ibid.*). Furthermore, the particular sequence identified by the Office contains five hydrophobic residues (one each of Val, Leu, and Ile, and two Ala residues) out of a total of eight, and would not be expected to be antigenic.

Even if, arguendo, the combined references taught the use of the cited sequence as an immunogen, only "0/4 to 3/4 of anti-peptide antibodies will bind to the native antigen" (Harlow and Lane, *ibid.*). In contrast, inherency must be certain. *Ex parte Cyba* (*ibid.*).

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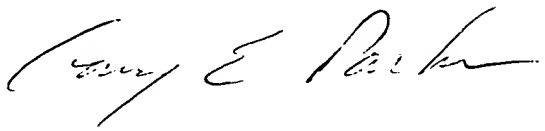
Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102 (e) are requested.

Applicant believes that each rejection has been addressed and overcome. Reconsideration of the application and its allowance are requested. If for any reason the Examiner feels that a telephone conference would expedite prosecution of the application, the Examiner is invited to telephone the undersigned at (206) 442-6673.

Respectfully Submitted,



Gary E. Parker
Registration No. 31,648

Enclosures:

Amendment Fee Transmittal (in duplicate)
Request for Extension of Time
Appendix
3 References
Postcard

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Appendix

At page 1, lines 5-6, please replace the title with the following:

ANTIBODIES TO SERINE PROTEASE POLYPEPTIDES [AND MATERIALS AND METHODS FOR MAKING THEM]

At page 41, please replace the paragraph at lines 5-14 with the following:

The results showed that Zsig13 maps 417.10 cR_3000 distal from the top of the human chromosome 11 linkage group on the WICGR radiation hybrid map. Proximal and distal framework markers were D11S1979 and D11S2384, respectively. The use of surrounding markers positions Zsig13 in the 11q22.1 region on the integrated LDB chromosome 11 map (The Genetic Location Database, University of Southhampton, WWW server: [http://]cedar.genetics. soton.ac.uk/public_html/). This region of chromosome 11 is fairly rich in proteases.

At page 47, please replace the title with the following:

ANTIBODIES TO SERINE PROTEASE POLYPEPTIDES [AND MATERIALS AND METHODS FOR MAKING THEM]

Please replace the Abstract of the Disclosure with the following:

[A novel serine protease is disclosed. The protease comprises a sequence of amino acid residues that is at least 95% identical to SEQ ID NO:2 from Ile, residue 111, through Asn, residue 373. Also disclosed are polynucleotide molecules encoding the protease, expression vectors containg the polynucleotides, cultured cells containing the expression vectors, and methods of making the protease. The protease can be used, *inter alia*, within industrial processes to degrade unwanted proteins or alter the characteristics of protein-containing compositions.] Antibodies that specifically bind to novel serine protease polypeptides are disclosed. The polypeptides are selected from the group consisting of a polypeptide as shown in SEQ ID NO:2 from residue 1 through residue 373, a polypeptide as shown in SEQ ID NO:15 from residue 1 through residue 373, and a polypeptide as shown in SEQ ID NO:18 from residue 1 through residue 364.